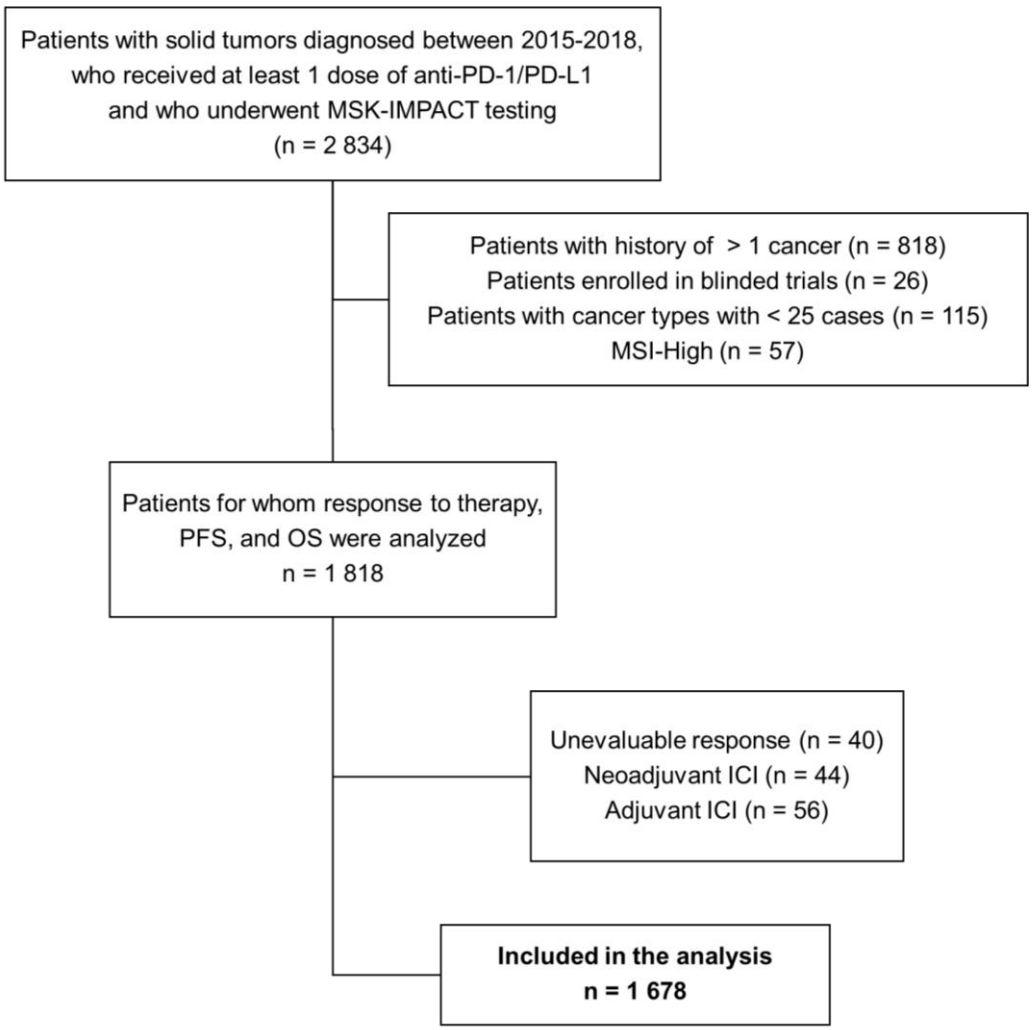
Supplementary Online Content

Valero C, Lee M, Hoen D, et al. Response rates to anti–PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. *JAMA Oncol.* Published online February 18, 2021. doi:10.1001/jamaoncol.2020.7684

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram



Abbreviations: MSI, microsatellite instability; PFS, progression-free survival; OS, overall survival; ICI, immune checkpoint inhibitors

eTable 1. Characteristics of Patients in the Study

Characteristic	No. patients (%)
Sex	
Female	754 (44.9)
Male	924 (55.1)
Age, median, years (IQR)	64 (55-71)
Cancer type	
NSCLC	663 (39.5)
Melanoma	214 (12.8)
Renal	92 (5.5)
Sarcoma	84 (5.0)
Bladder	82 (4.9)
Head and Neck	74 (4.4)
Gastric	67 (4.0)
SCLC	54 (3.2)
Hepatobiliary	53 (3.2)
Colorectal	50 (3.0)
Endometrial	47 (2.8)
Esophageal	45 (2.7)
Pancreatic	36 (2.2)
Mesothelioma	35 (2.1)
Ovarian	29 (1.7)
Unknown primary	28 (1.7)
Breast	25 (1.5)
Drug class	
PD-1/PD-L1	1392 (83.0)
Combo	286 (17.0)
Prior chemotherapy	
No	509 (30.3)
Yes	1141 (68.0)
Unknown	28 (1.7)
Stage	
I-III	99 (5.9)
IV	1548 (92.3)
Unknown	31 (1.8)
Year of treatment	
2015-2016	443 (26.4)
2017-2018	1235 (73.6)

Abbreviations: NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer

Combo, patients who received both an anti-PD-1/PD-L1 and an anti-CTLA-4 drug in the same line of treatment

eTable 2. Cancer Type–Specific Cutoffs for High Tumor Mutational Burden (TMB)

Cancer type	Cutoff (AUC)	TMB-low No. patients (%)	TMB-high No. patients (%)
NSCLC	13.90 (0.58)	545 (82.2)	118 (17.8)
Melanoma	20.80 (0.65)	148 (69.2)	66 (30.8)
Renal	5.10 (0.58)	69 (75.0)	23 (25.0)
Sarcoma	3.70 (0.61)	62 (73.8)	22 (26.2)
Bladder	7.45 (0.71)	40 (48.8)	42 (51.2)
Head and Neck	8.35 (0.57)	56 (75.7)	18 (24.3)
Gastric	6.00 (0.56)	49 (73.1)	18 (26.9)
SCLC	11.85 (0.63)	41 (75.9)	13 (24.1)
Hepatobiliary	1.90 (0.62)	11 (20.8)	42 (79.2)
Colorectal	8.35 (0.88)	36 (72.0)	14 (28.0)
Endometrial	7.00 (0.54)	33 (70.2)	14 (29.8)
Esophageal	7.90 (0.45)	36 (80.0)	9 (20.0)
Pancreatic	2.30 (0.64)	10 (27.8)	26 (72.2)
Mesothelioma	2.60 (0.39)	23 (65.7)	12 (34.3)
Ovarian	4.40 (0.65)	22 (75.9)	7 (24.1)
Unknown primary	6.00 (0.71)	20 (71.4)	8 (28.6)
Breast	5.70 (0.83)	20 (80.0)	5 (20.0)

Optimized cutoffs points based on Receiver Operating Characteristic (ROC) curves using Youden method.

Abbreviations: AUC, Area under the curve; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

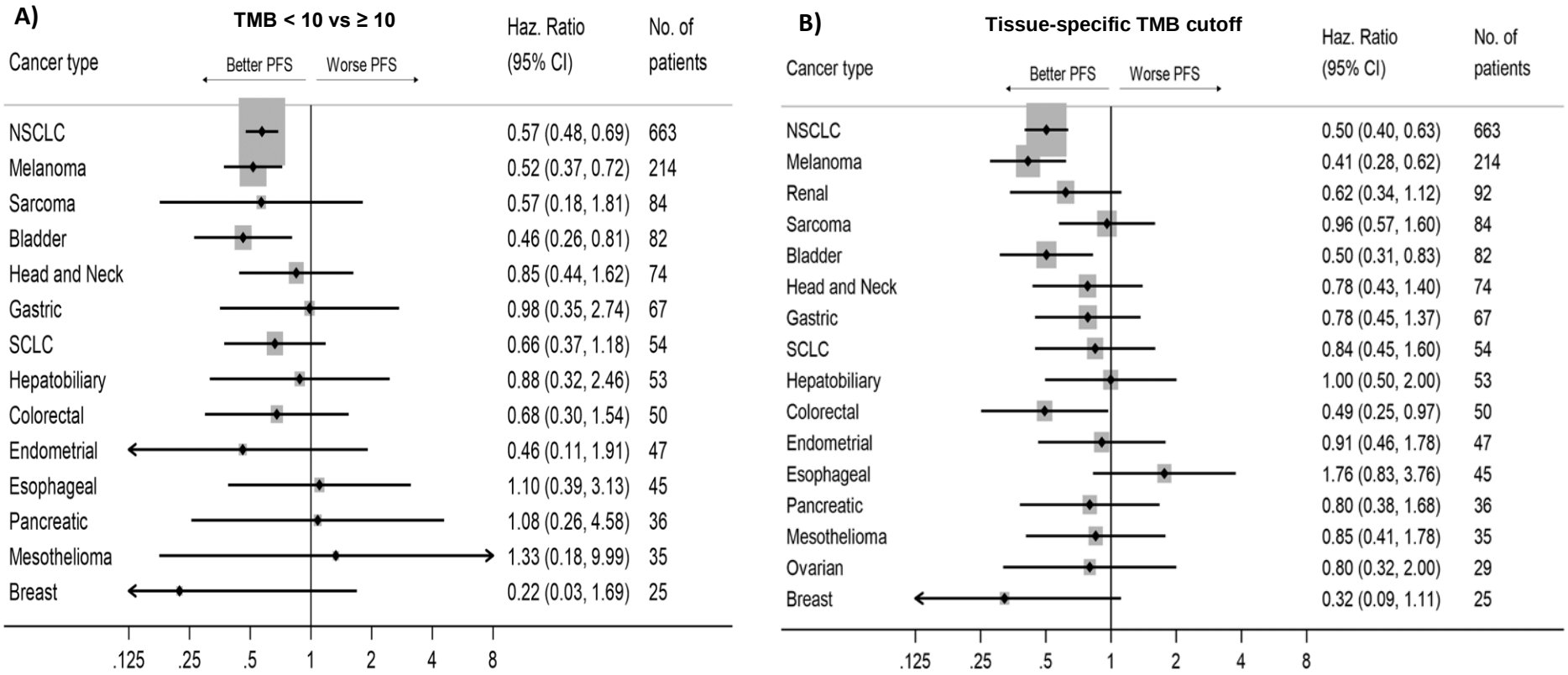
eTable 3. Odds Ratios (ORs) of Response Based on Tumor Mutational Burden (TMB) by Cancer Type

	OR	95% CI
TMB high vs low		
NSCLC	2.06	1.43-2.97
Melanoma	2.92	1.67-5.12
Renal		
Sarcoma	15.46	1.49-160.48
Bladder	5.40	1.59-18.35
Head and Neck	1.64	0.44-6.19
Gastric	0.57	0.06-5.40
SCLC	2.03	0.53-7.72
Hepatobiliary		
Colorectal	3.42	0.27-43.70
Endometrial	7.78	0.63-95.68
Esophageal	2.15	0.27-17.02
Pancreatic		
Mesothelioma		
Ovarian		
Breast		

Odds Ratios with 95% CIs for response across cancer types comparing TMB-high vs low. TMB stratified into high and low using 10 mutations/megabase as cutoff for all cancer types. Odds Ratios not shown for cancer types with unstable models. For Renal cancer, Odds Ratio not shown due to the absence of patients in the TMB-high group.

Abbreviations: CI, Confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

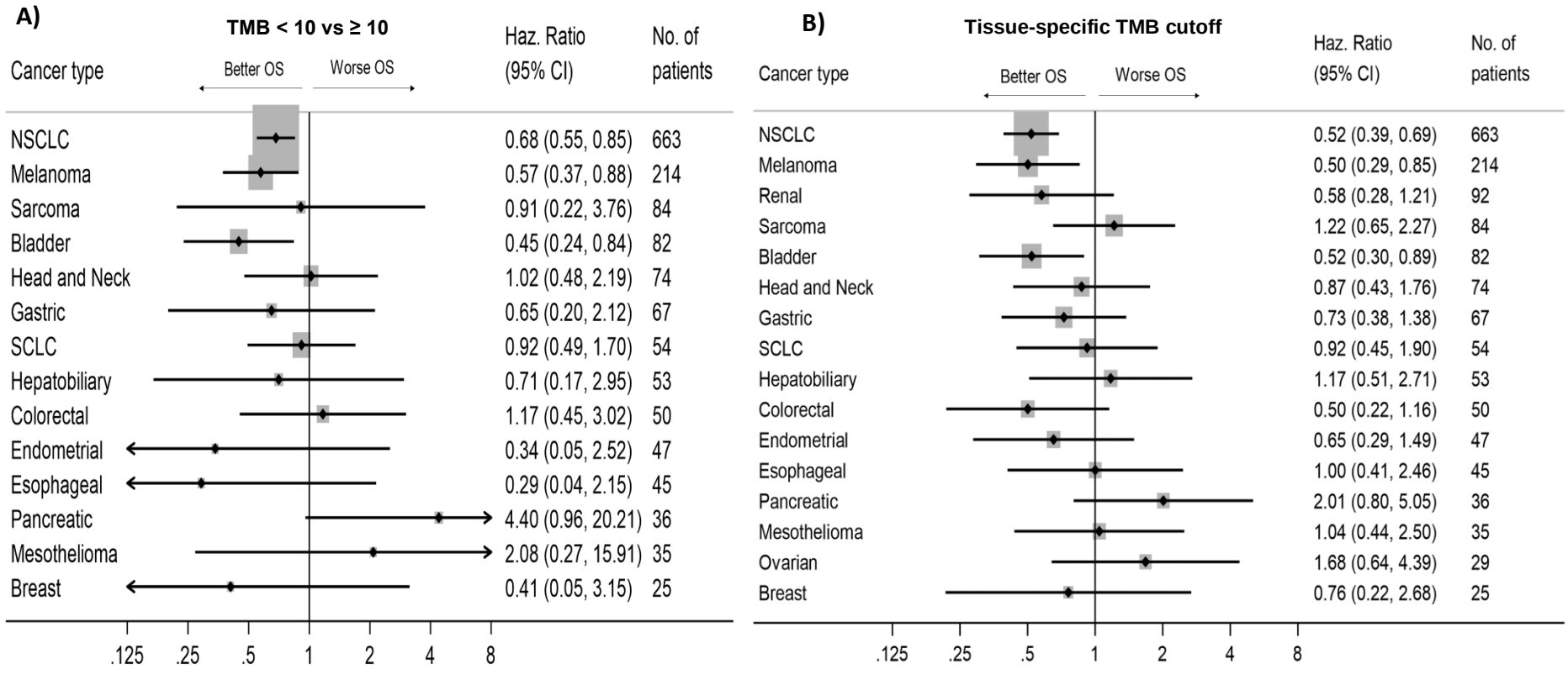
eFigure 2. Progression-Free Survival (PFS) Based on Tumor Mutational Burden (TMB) by Cancer Type



Forest plots showing hazard ratios with 95% CIs for PFS comparing A) TMB <10 mut/Mb to ≥ 10 mut/Mb and B) TMB-Low to TMB-High using cancer type-specific cutoffs using the Youden method. In the forest plot for TMB <10 mut/Mb vs ≥ 10 mut/Mb renal cancer is not shown due to the absence of patients in the TMB ≥ 10 mut/Mb group, and ovarian cancer is not shown due to instability of the model.

Abbreviations: NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer

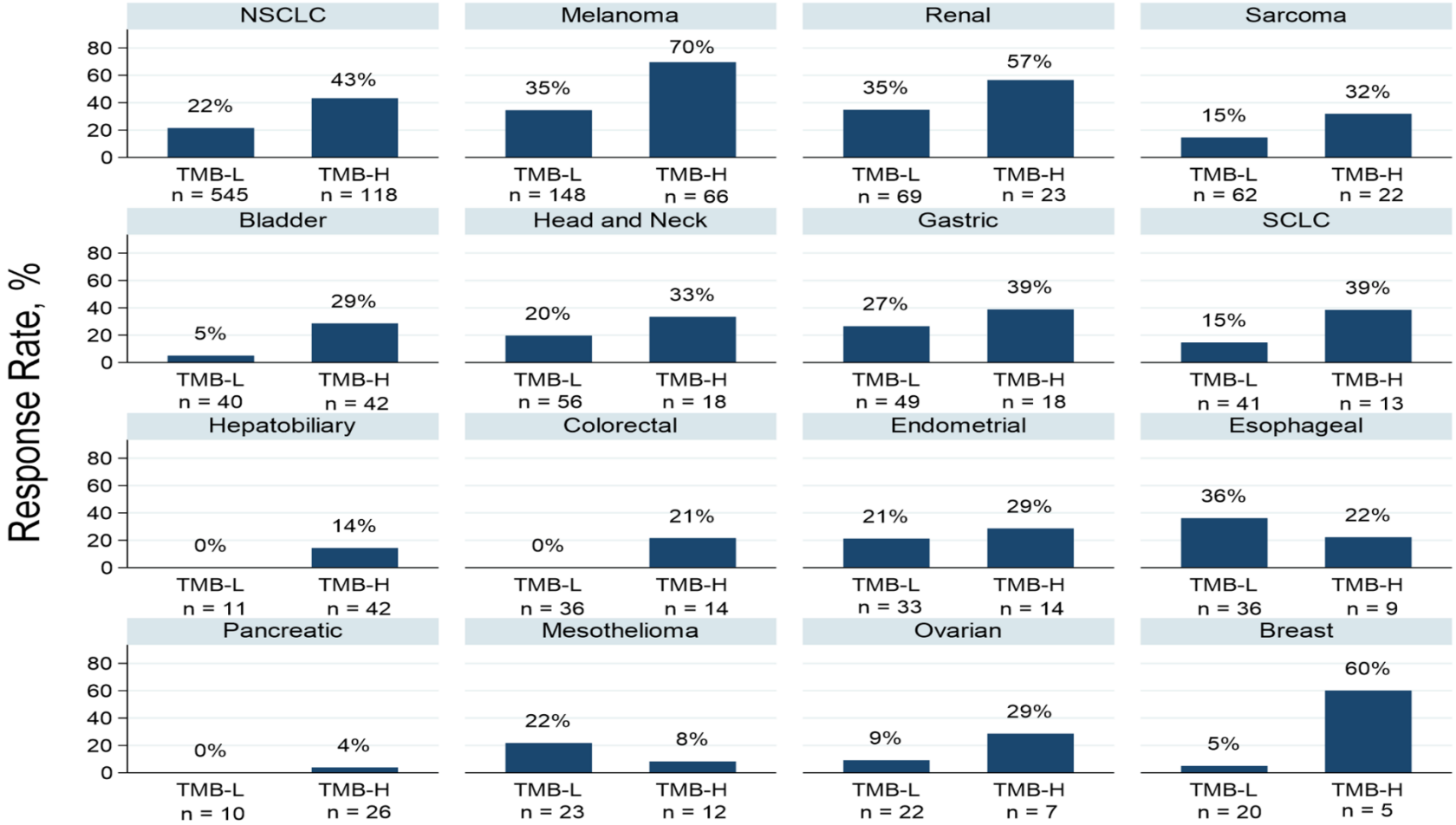
eFigure 3. Overall Survival (OS) Based on Tumor Mutational Burden (TMB) by Cancer Type



Forest plots showing hazard ratios with 95% CIs for OS comparing A) TMB <10 mut/Mb to ≥ 10 mut/Mb and B) TMB-Low to TMB-High using cancer type-specific cutoffs using the Youden method. In the forest plot for TMB <10 mut/Mb vs ≥ 10 mut/Mb renal cancer is not shown due to the absence of patients in the TMB ≥ 10 mut/Mb group, and ovarian cancer is not shown due to instability of the model.

Abbreviations: NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer

eFigure 4. Response Rates Based on Tumor Mutational Burden (TMB) by Cancer Type Using Tissue-Specific Cutoffs



TMB stratified into high and low using cancer type-specific cutoffs found with Receiver Operating Characteristic (ROC) curves and Youden method for each cancer type.

Abbreviations: NSCLC, Non-small cell lung cancer; TMB-L, tumor mutational burden low; TMB-H, tumor mutational burden high; SCLC, small cell lung cancer

eTable 4. Outcomes for Cancer Types Previously Lacking a United States Food and Drug Administration (FDA) Approval for Treatment With Immune Checkpoint Inhibitors (ICIs)

	Non-responders No. patients (%)	Responders No. patients (%)	Response OR (95% CI)	PFS HR (95% CI)
FDA cutoff				
< 10 mut/Mb	235 (89.4)	28 (10.6)	Ref	Ref
≥ 10 mut/Mb	16 (72.7)	6 (27.3)	3.15 (1.14-8.70)	0.65 (0.41-1.03)

Abbreviations: OR, Odds Ratio; CI, confidence interval; PFS, progression-free survival; HR, hazard ratio; mut, mutations; Mb, megabase; Ref, reference